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STATE-OF-THE-ART PAPER

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Device Therapy in Heart Failure Patients With CKD

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Leon A. Cannizzaro, Jonathan P. Piccini, Uptal D. Patel, Adrian F. Hernandez

Heart failure and chronic kidney disease (CKD) both carry significant risk for sudden cardiac death, hospitalization, and mortality; when combined, the risks may be multiplied. However, many of the major trials demonstrating the benefits of implantable cardioverter-defibrillators (ICDs) and cardiac resynchronization therapy (CRT) excluded patients with significant CKD. In this review, Cannizzaro and colleagues discuss the intersection of heart failure and CKD as it relates to progressive heart failure and the risk of sudden death. There appears to be a need for dedicated clinical trials and comparative effectiveness studies to identify the appropriate use of ICD and CRT devices in patients with heart failure and CKD.

CLINICAL RESEARCH

CLINICAL TRIALS

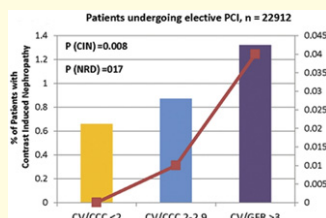
hANP Infusion May Protect the Renal Function in Patients Undergoing CABG

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Akira Sezai, Mitsumasa Hata, Tetsuya Niino, Isamu Yoshitake, Satoshi Unosawa, Shinji Wakui, Haruka Kimura, Motomi Shiono, Tadateru Takayama, Atsushi Hirayama

Sezai and colleagues studied the ability of human atrial natriuretic peptide (hANP) infusion to prevent acute kidney injury in patients with chronic kidney disease (CKD) undergoing coronary artery bypass grafting (CABG). Patients with pre-operative CKD (pre-operative estimated glomerular filtration rate <60 ml/min/1.73 m²) undergoing CABG were randomized to hANP infusion or placebo. The post-operative serum creatinine was significantly lower in the hANP group not only at 1 month, but also at 1 year. There were fewer cardiac events and patients receiving chronic dialysis in the hANP group at 1 year. hANP infusion appears to protect and preserve renal function in patients with CKD undergoing CABG.

Editorial Comment: Guido Boerrigter, John C. Burnett, Jr, p. 904



INTERVENTIONAL CARDIOLOGY

New Formula for Predicting Safe Amount of Contrast Media in Patients Undergoing PCI 907

Hitinder S. Gurm, Simon R. Dixon, Dean E. Smith, David Share, Thomas LaLonde, Adam Greenbaum, Mauro Moscucci, for the BMC2 (Blue Cross Blue Shield of Michigan Cardiovascular Consortium) Registry

The association between calculated creatinine clearance (CCC)-based contrast dose and the risk of contrast-induced nephropathy (CIN) and nephropathy requiring dialysis (NRD) was assessed by Gurm and colleagues in nearly 60,000 patients undergoing percutaneous coronary intervention (PCI). The risk of CIN and NRD was directly associated with increasing contrast volume adjusted for CCC. The risk for CIN and NRD approached significance when the ratio of contrast dose/CCC exceeded 2, and the risk was dramatically elevated in patients exceeding a ratio of 3. Limiting contrast volume to <3 times the CCC prevents the vast majority of cases of post-PCI CIN.

HEART FAILURE

Impact of Beta-Blockers on Mortality for HF Questioned in U.S. Patients 915

Christopher M. O'Connor, Mona Fiuzat, Karl Swedberg, Michael Caron, Bruce Koch, Peter E. Carson, Wendy Gattis Stough, Gordon W. Davis, Michael R. Bristow

O'Connor and colleagues performed a meta-analysis of the large, randomized, double-blind, placebo-controlled studies that: 1) evaluated beta-blockers in heart failure (HF) patients; 2) had a primary endpoint of mortality; and 3) enrolled U.S. patients. Nearly 9,000 patients were enrolled in the MERIT-HF (Metoprolol Controlled-Release Randomized Intervention Trial in Heart Failure), COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival), and BEST (β -Blocker Evaluation of Survival Trial) studies combined; 47% were from the United States. The mortality reduction associated with beta-blockade in the U.S. cohort was small and not statistically significant (relative risk [RR]: 0.92), but the reduction was significant in the rest of the world cohort (RR: 0.64). The authors conclude by exploring various hypotheses to explain these differences, but they arrive at no firm answers.

Editorial Comment: Barry M. Massie, p. 923

HEART FAILURE

Outcomes of Patients With X-Linked DCM Caused by Defects in the DYS Gene 925

Marta Diegoli, Maurizia Grasso, Valentina Favalli, Alessandra Serio, Fabiana Isabella Gambarin, Catherine Klersy, Michele Pasotti, Emanuela Agozzino, Laura Scelsi, Alessandra Ferlini, Oreste Febo, Giovanni Piccolo, Luigi Tavazzi, Jagat Narula, Eloisa Arbustini

Diegoli and colleagues describe the diagnostic work-up, phenotype, and long-term outcomes of patients with a dilated cardiomyopathy (DCM) associated with genetic defects in the dystrophin (DYS) gene. Over 400 consecutive male patients with DCM underwent a standardized evaluation, including a thorough sequencing of the DYS gene. DYS defects were found in 8%, 90% of whom had proven X-linked inheritance. Most patients also had a mild skeletal myopathy and/or increased serum creatine phosphokinase (sCPK). During a median follow-up of 5 years, 23% of these patients underwent transplantation and 26% died of heart failure, but none had evidence of life-threatening ventricular arrhythmias. DYS-related DCM should be suspected in male patients with increased sCPK and X-linked inheritance.

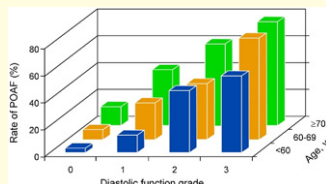
CARDIAC RESYNCHRONIZATION THERAPY**Meta-Analysis Confirms Benefit of CRT in Minimally Symptomatic HF Patients****935***Selcuk Adabag, Henri Roukoz, Inder S. Anand, Arthur J. Moss*

Adabag and colleagues performed a systematic review and meta-analysis of prospective randomized clinical trials of cardiac resynchronization therapy (CRT) versus implantable cardioverter-defibrillators (ICDs) in patients with reduced ejection fraction (EF), prolonged QRS interval, and New York Heart Association (NYHA) functional class I to II heart failure (HF). Data was combined from 5 clinical trials, including 4,317 patients with NYHA functional class I to II HF. All-cause mortality was significantly reduced with CRT compared with ICD (relative risk [RR]: 0.81). This benefit was significant for patients with NYHA functional class II, but not for NYHA functional class I; however, NYHA functional class I patients had an RR of 0.57 for HF hospitalization with CRT. These results confirm the benefits of CRT in minimally symptomatic or asymptomatic patients.

HEART RHYTHM DISORDERS**Stringency of Rate Control Does Not Affect Cardiac Remodeling in Patients With Permanent AF****942***Marcelle D. Smit, Harry J. G. M. Crijns, Jan G. P. Tijssen, Hans L. Hillege, Marco Alings, Ype S. Tuininga, Hessel F. Groenveld, Maarten P. Van den Berg, Dirk J. Van Veldhuisen, Isabelle C. Van Gelder, for the RACE II Investigators*

Smit and colleagues evaluated echocardiographic remodeling in permanent atrial fibrillation (AF) patients treated with either lenient or strict rate control. Echocardiography was conducted at baseline and at follow-up in 517 patients randomized to strict heart rate control (target <80 beats/min) or lenient rate control (target <110 beats/min). Between baseline and follow-up, significant adverse atrial or ventricular remodeling was not observed in either group. This was also true when stratified by actual achieved heart rates rather than targeted rates. These results suggest that lenient rate control does not increase the risk of adverse cardiac remodeling in patients with permanent AF.

Editorial Comment: D. George Wyse, p. 950

**CARDIAC SURGERY****Diastolic Function Strongly Linked to Risk of POAF****953**

Rowlens M. Melduni, Rakesh M. Suri, James B. Seward, Kent R. Bailey, Naser M. Ammash, Jae K. Oh, Hartzell V. Schaff, Bernard J. Gersh

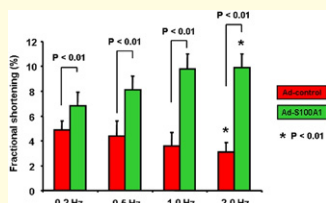
Melduni and colleagues investigated whether left ventricular (LV) diastolic dysfunction was an important risk factor for post-operative atrial fibrillation (POAF) after cardiac surgery. Patients were residents of Olmsted County, Minnesota, who underwent complete LV diastolic function assessment prior to cardiac surgery. POAF occurred in 38% of patients. The rate of POAF increased exponentially with diastolic function grade. LV diastolic dysfunction is a powerful, independent predisposing substrate for the initiation of POAF; targeting interventions at the highest-risk groups may help to identify prophylactic measures.

VALVULAR HEART DISEASE**Valvular Aortic Stenosis Commonly Develops After Surgery for Subaortic Stenosis** **962**

Zachary W. M. Laksman, Candice K. Silversides, Tara Sedlak, Ahmed M. Samman, William G. Williams, Gary D. Webb, Peter P. Liu

Classic teachings emphasize that patients with discrete subaortic stenosis are at risk for later aortic regurgitation because the high velocity jet may damage the valve. Laksman and colleagues reviewed the records of 121 adults with a diagnosis of congenital discrete fibromuscular subaortic stenosis, most of whom had previously undergone surgery. Valvular aortic stenosis requiring surgery developed in 26%, while only 3% required surgery for aortic insufficiency. The risk of developing aortic stenosis was higher in patients with a bicuspid aortic valve, coarctation of the aorta, and/or supra-ventricular stenosis.

PRE-CLINICAL RESEARCH



PRE-CLINICAL RESEARCH

Genetically Increasing S100A1 Reverses Dysfunction of Failing Human Cardiomyocytes

966

Henriette Brinks, David Rohde, Mirko Voelkers, Gang Qiu, Sven T. Pleger, Nicole Herzog, Joseph Rabinowitz, Arjang Ruhparwar, Scott Silvestry, Carolin Lerchenmüller, Paul J. Mather, Andrea D. Eckhart, Hugo A. Katus, Thierry Carrel, Walter J. Koch, Patrick Most

Translational studies in animal heart failure (HF) models have identified S100A1 as a unique regulator of an integrative Ca^{2+} controlled network in cardiomyocytes involving sarcoplasmic reticulum and sarcomeric and mitochondrial functions. Brinks and colleagues obtained cardiomyocytes from failing human hearts and confirmed lower levels of S100A1; these cells were then transfected to express higher levels of S100A1. S100A1 gene therapy both reversed contractile dysfunction and improved contractile reserve under beta-adrenergic receptor stimulation. S100A1 reversed underlying Ca^{2+} handling abnormalities, improved mitochondrial function, and restored the phosphocreatine/adenosine-triphosphate (ATP) ratio. These findings strengthen the rationale for future molecular-guided therapy of human HF using S100A1.

Editorial Comment: Stephen L. Belmonte, Kenneth B. Margulies, Burns C. Blaxall, p. 974

PRE-CLINICAL RESEARCH

Combination of IGF-1 and HGF Stimulates Endogenous Cardiac Stem Cells After Infarct in Porcine Model

977

Georgina M. Ellison, Daniele Torella, Santo Dellegrattaglia, Claudia Perez-Martinez, Armando Perez de Prado, Carla Vicinanza, Saranya Purushothaman, Valentina Galuppo, Claudio Iaconetti, Cheryl D. Waring, Andrew Smith, Michele Torella, Carlos Cuellas Ramon, Jose Manuel Gonzalo-Orden, Valter Agosti, Ciro Indolfi, Manuel Galiñanes, Felipe Fernandez-Vazquez, Bernardo Nadal-Ginard

Ellison and colleagues tested the ability of a combination of insulin-like growth factor (IGF)-1 and hepatocyte growth factor (HGF) to activate resident endogenous porcine cardiac stem/progenitor cells (epCSCs) and to promote myocardial repair in a pig model of myocardial infarction (MI). Acute MI was induced by transient balloon occlusion. IGF-1 and HGF were then coadministered through the infarct-related artery 30 min after coronary reperfusion. IGF-1/HGF activated epCSCs increased their myogenic differentiation, improved cardiomyocyte survival, reduced fibrosis, and were associated with reduced infarct size and improved ejection fraction at 2 months. These cofactors appear to stimulate epCSCs in a method that is simpler and more clinically relevant than other attempts to use stem cell therapy to treat acute MI.

